REMARKS

1. Compliance with Sequence Rules (OA §5)

A substitute sequence listing is enclosed which addresses Fig. 2, and conforming amendments have been made to the brief description of the drawings..

1.1. Applicants hereby submit the following:

a paper copy of a "Sequence Listing", complying with §1.821(c), to be incorporated into the specification as directed above;

the Sequence Listing in computer readable form, complying with §1.821(e) and §1.824, including, if an amendment to the paper copy is submitted, all previously submitted data with the amendment incorporated therein;

since this response is being e-filed, the ASCII text file attached hereto should be used as both the paper copy and the CRF, in accordance with EFS practice.

1.2. The undersigned attorney or agent hereby states as follows:

(a) this submission does not include new matter [§1.821(g)];

(b) the contents of the paper copy (as amended, if applicable) and the computer readable form of the Sequence Listing, are the same [§1.821(f) and §1.825(b)];

(c) if the paper copy has been amended, the amendment is supported by the specification and does not include new matter [§1.825(a)];

(d) if the computer readable form submitted herewith is a substitute for a form found upon receipt by the PTO to be damaged or unreadable, that the substitute data is identical to that originally filed [§1.825(d)]; and

(e) if reliance is made on a computer readable form presented in a prior application, the paper copy in this application is identical to the CRF in the prior application [§1.821(e)].

1.3. Under U.S. rules, each sequence must be classified in <213> as an "Artificial Sequence", a sequence of "Unknown" origin, or a sequence originating in a particular organism, identified by its scientific name.

Neither the rules nor the MPEP clarify the nature of the relationship which must exist between a listed sequence and an organism for that organism to be identified as the origin of the sequence under <213>.

Hence, counsel may choose to identify a listed sequence as associated with a particular organism even though that sequence does not occur in nature by itself in that organism (it may be, e.g., an epitopic fragment of a naturally occurring protein, or a cDNA of a naturally occurring mRNA, or even a substitution mutant of a naturally occurring sequence). Hence, the identification of an organism in <213> should not be construed as an admission that the sequence *per se* occurs in nature in said organism.

Similarly, designation of a sequence as "artificial" should not be construed as a representation that the sequence has no association with any organism. For example, a primer or probe may be designated as "artificial" even though it is necessarily complementary to some target sequence, which may occur in nature. Or an "artificial" sequence may be a substitution mutant of a natural sequence, or a chimera of two or more natural sequences, or a cDNA (i.e., intron-free sequence) corresponding to an intron-containing gene, or otherwise a fragment of a natural sequence.

The Examiner should be able to judge the relationship of the enumerated sequences to natural sequences by giving full

consideration to the specification, the art cited therein, any further art cited in an IDS, and the results of his or her sequence search against a database containing known natural sequences.

2. Overview of Claim Amendments

2.1. Claim 8 has been amended to clarify the "fragment or variant" language.

Clause (I) defines four types of peptides. In (a), we have the peptides of SEQ ID NOs:1-4, 7, 10-18, 40 or 41. In (b), we have fragments of (a) that are long enough to satisfy at least one of the functional limitations (i)-(v) and are at least 5 amino acids long. Clauses (a) and (b) have basis in original claim 8. The lengths of the SEQ ID NO sequences are 5-16 amino acids, and P24, L17 contemplates deletion of up to 10 amino acids. Hence we require a minimum of 5 amino acids. See also P25, L8.

In (c), we have peptides which consist of a peptide of (a) and up to 10 additional amino acids. Basis for (c) is at P24, L17-18.

In (d) we allow substitution mutants of (a)-(c), with basis at P21, L21 and 31-35. The minimum homology limitations are based on P25, L7-12.

These mutants must either retain at least five consecutive amino acids of a peptide of (a), or comprises a sequence at least 50% identical to a peptide of (a). We assume that deletion of any amino acid, as in the case of a fragment, reduces the percentage identity, just as does replacement of an amino acid of such a peptide.

Clause (II) addresses oligomers or polymers of the peptides of (I), with basis at P21, L22-30.

To be an oligomer or polymer, the compound must of course comprise a plurality of such peptides in addition, we require that it either consist of such peptides or comprise a non-NCAM

carrier moiety to which said peptides are attached.

We have also deleted SEQ ID NO:3 from claim 8, clause (I)(a), and cancelled claim 11, because P87, L1-3 taught that this peptide was non-inhibitory.

2.2. Claims 9, 10 and 12-35 have been amended to use the "closed" transition "consisting of".

2.3. Basis for new claims:

44: Claim 7
45-48 P21, L23-30
49: original claim 8
50: P25, L16
51: P21, L34
52: P22, L1-P23, L23
53: as above, note "at least one"
54-57: P24, L17-21
58-59: original claim 8
60-62: P21, L22-30. Both homooligomers ("repetitive sequences", P21, L24) and heterooligomers (implied by the "and/or" in P50, L24-P51, L2) are contemplated.
64-65: see discussion of claim 8.

3. Claim Objections(OA §6)

We have amended claim 8 to identify "NCAM" as an abbreviation for neural (not nuclear) cell adhesion molecule. See P1, L25.

4. Definiteness (OA §8)

We have deleted the limitation "wherein said peptide is selected by the method according to claim 20", as it creates a circular reference (claim 20 being dependent on claim 8).

The reference should have been to claim 7 but in any event we have moved it to a new dependent claim (44).

5. Prior Art Issues (OA §§11-12)

The examiner says at the bottom of page 9:

> Claims 8-10, 12-14, 16, 17, 19-26 and 41 are rejected under 35 U.S.C.. 102(b) as being anticipated by NCBI Accession polypeptide as first submitted by Small et al. (J. Cell Biol. 105:2335-2345 (1987) and identified as P13596.
>
> Small et al. teach the identification of the full length NCAM polypeptide from rat. Said sequence is 100% identical to the instant SEQ ID NOs:1, 2, 4-6, 8, 9 and 11-26.
>
> It is noted that the limitations of the indicated claims and the recitation of "having" is interpreted as being open comprising language. Thus, said polypeptide as taught by Small et al./NCBI Accession P13596 is asserted to inherently be capable of binding to the NCAM homolyphic binding site composed of lg1-2-3.

The term "having", which is sometimes interpreted as "open-ended", appears in claims 9-35 and not in claim 8. Claims 9-35 are dependent on 8 and therefore cannot be broader than 8. However, to avoid any ambiguity, we have replaced "having" with --consisting of--.

Small teaches full length NCAM, which is 858 amino acids long (per the cited P13596), and hence it is misleading to state that "said sequence is 100% identical to the instant SEQ ID Nos" of clause (I)(a). Rather, it merely comprises those peptides. In general, a large molecule is not considered anticipatory of smaller molecules that it comprises, absent a specific teaching that those fragments of the larger molecule be prepared.

For like reasons, Small is not anticipatory of the fragments of those peptides, enunciated in clause (I)(b).

The prior term "variants" is admittedly susceptible of broad interpretation. Amended claim 8 covers the variants in

clauses (I)(c), (I)(d) and (II).

Clause (I)(c) permits addition of up to 10 amino acids. Since the largest sequence of clause (I)(a) is 16 amino acids, (I)(c) permits up to 26 amino acids. That is still well short of any peptide contemplated by Small.

Clause (I)(d) covers substitution mutants of (I)(a)-(c). Substitution of amino acids of course leaves the length unchanged.

Finally, clause (II) covers polymers and oligomers of the peptides of (I). While the peptides of clause (II) are larger than those of clause (I), they are also required to either consist of a plurality of sequences of those peptides, or to comprise a non-NCAM carrier moiety. We respectfully assert that claim 8, as amended, is not anticipated by Small.

6. Written Description (OA §9-10)

The Examiner argued that we were claiming a generic class of molecules with merely a defined function. We have now amended the claim to replace the prior recitation of "fragments and variants" with clauses imposing meaningful structural limitations, i.e., limiting the number of additions, deletions and substitutions relative to the recited sequences.

It is true, of course, that the species of SEQ ID NOs:1-18, 40 and 41 share no common structure. But it would not be expected that peptides that disrupt Ig1:Ig3 interaction would also disrupt Ig2:Ig2 interaction (or vice versa), and for that matter a peptide could disrupt Ig1:Ig3 interaction either by binding to Ig1 or Ig3. Even those binding a single module could bind to different, non-overlapping sites. So the lack of common structure doesn't seem to be a meaningful criticism.

The table below identifies the module (Ig1, Ig2 or Ig3) with which the recited sequences are associated.

SEQ ID NO:	Positioned in
1	Ig1
2	Ig1
4	Ig2
7	Ig2
10	Ig2
11	Ig3
12	Ig3
13	Ig3
14	Ig2
15	Ig2
16	Ig2
17	Ig2
18	Ig2
40	Ig1
41	Ig1

The peptides may also be characterized in terms of their contacts, e.g., from pp. 86-88:

Ig1-to-Ig3	P1-CD (SID 40) P1-FG (SID 41) (controls SID 24)
Ig2-to-Ig2	P2-A'B (SID 17)
Ig2-to-Ig3	(SID 13) (controls SID 26, 27, 3)

The sequences of clause (I)(a) are fully defined and thus fall within the "safe haven" of written description practice. (cp. new claim 59).

The longer peptides of clause (I)(c) are justifiable in

that the Written Description Training Materials generally take the position that if "SEQ ID NO:X" has written description, a "protein comprising SEQ ID NO:X" likewise has written description. Note that (I)(c), unlike the examples in the WDTM, limits the number of additional amino acids.

With regard to the shorter peptides of clause (I)(b), the sequences of clause (I)(a) are of course themselves fragments of NCAM modules Ig1, Ig2 or Ig3. The skilled worker would consider applicants to have possession, based on the teachings at P18, L30-31 and P24, L17-19, of fragments. Applicants disclose the complete 3D structure of NCAM (Fig. 2 and P79) and teach how to use this structure in designing interacting compounds (pp 46-50). The inter domain interactions are discussed at PP 61-63, and all this can be compared with the "interaction interface peptides" discussed at P86-87.

From this, it can be concluded whether a particular fragment of (I)(c) is likely to inhibit NCAM adhesion.

With regard to the mutants of (I)(d), we first have the general teachings as to desired percentage identity (P20, L16-P21, L2; P25, L7-17) and conservative substitution (P21, L35-P23, 23).

Next, we have the aforementioned 3D structure, which reveals residues appearing in the interdomain interface, and also their involvement in secondary structure.

We also have the experimental guidance, including some mutational analysis.

We know from the experiment described at P85, L17-25 that recombinant wild type Ig3 module (Ig3wt) inhibits NCAM adhesion (presumably by interaction with Ig1 and Ig2) whereas the mutants Ig3 mut 1 (R198A, D249G, E253A) and Ig3 mut 2 (K285A, F287A) do not have inhibitory activity.

We know from the experiment described at P87, L10-20 that

(1) P1-CD (SID 40) (Fig. 11) peptides inhibited NCAM-stimulated neurite outgrowth, presumably by mediation of the

Ig1-Ig3 contact (p86, L13-14)

(2) the same was true of P3-DE (SID 20) (not presently claimed) but P3-DE-trunc (10 a.a. shorter) was not inhibitory (Fig. 6)

(3) P3-G (SID 12) was inhibitory (Fig. 6), presumably by mediation of the Ig2-Ig3 contact (P86, L26-31), but P3-G-K285A-F2875 (SID 26), P3-G-K285A-F287G (SID 27) (P86, L31-35), and P3-B (SID 3) (P87, L1-3) were not.

(4) the peptide P2-A'B (SID 17) (P86, L24-25) modulated neurite outgrowth but did not stimulate differentiation of single CGN in primary culture. (P87, L17-20).

With regard to oligomers or polymers of (II), it is well known in the immunological art that such compounds can interact with a target much as would the component monomer, and with greater potency.

Given the proposed claim limitations, the clear WD for the recited sequences, the in silico analysis made possible by the 3D structure, and the exemplified mutational analysis in vitro, there is WD for the proposed amended claims, which require common structural features with at least one of the exemplified peptides, albeit not with all of them.

Should the examiner not be persuaded that claim 8 satisfies written description, consideration should be given to the new dependent claims.

If the problem is with clause (II), claims 45-48 and 60-63 limit its scope, and claims 49-59 eliminate it altogether.

If the problem is with the mutants of clause (I)(d), claims 50-53 and 63 limit its scope, and claims 58, 59, 64 and 65 eliminate them altogether.

If the problem is with the fragments of clause (I)(b), claims 54-57 limit its scope, and claims 59 and 65 eliminate them altogether.

If the problem is with the longer peptides of clause (I)(c), they are excised by claim 65.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant

By: _____
Iver P. Cooper
Reg. No. 28,005

Enclosure
--Sequence Listing TXT file

624 Ninth Street, N.W.
Washington, D.C. 20001
Telephone: (202) 628-5197
Facsimile: (202) 737-3528
IPC:lms
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